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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,825	09/10/2003	Jefferson C. Emery	39766-0113A	6061
35489 7590 12/28/2009 Arnold & Porter LLP (24126) Attn: IP Docketing Dept. 555 Twelfth Street, N.W. Washington, DC 20004-1206			EXAMINER AUDET, MAURY A	
			ART UNIT 1654	PAPER NUMBER
			MAIL DATE 12/28/2009	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/659,825

Applicant(s)

EMERY ET AL.

Examiner

MAURY AUDET

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 September 2009.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-25 and 27-46 is/are pending in the application.
4a) Of the above claim(s) 27-46 is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-25 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 10 September 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

As note previously, he present application has been transferred from former Examiner Shirali to the present Examiner.

Applicant's response (no amendments), arguments, are acknowledged.

The Examiner welcomes Applicant to telephone the Examiner and set up an interview, if this would be deemed helpful to Applicant.

Election/Restrictions

As noted previously, Applicant's election with traverse of Group I, claims 1-25, method of purifying a protein, in the reply filed on 2/1/07 is acknowledged. The traversal is on the ground(s) that, in summary, it would not be an undue burden since the former Examiner originally examined all the claims. This is not found persuasive for the reasons of record, and because restriction is proper at any time during prosecution, as warranted.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

The rejection of claims 1-25 under 35 U.S.C. 103(a) as being unpatentable over Genentech (Basey et al.; WO 99/57134) in view of Grandics et al. (US 5,571,720) and newly added reference, Winge (US 2001/0034053 A1, Priority Date 1/27/00), is maintained for the reasons of record. Applicant's arguments have been considered but are not found persuasive.

On page 14 of Applicant's response, Applicant's argument, summarized and stated in two different ways, is that the prior art does not teach/suggest protein purification via ion exchange chromatography by using different salt gradients during the washing phase; or stated the other way, washing using increasing salt concentration.

I. The Issue: Does the combination of references teach/suggest - provide motivation/predictability - that it would have been prima facie obvious for one of ordinary skill in the art to use different salt gradients during the washing phase/wash using increasing salt concentration (in standard, well known protein purification via ion exchange chromatography)?

II. Analysis of Prior Art References on these specific limitations:

i) Genentech (Basey et al.; WO 99/57134; see entire document, especially claims noted herein) teach method of purifying a peptide by ion exchange chromatography, by specifically modifying the concentration of any salt employed (claim 11), including specifically the concentration of NaCl as the salt (claim 13), as part of the multiple washing steps involved in eluting the desired protein (claims 1 and 23).

i) Winge et al. expressly teach increasing salt gradients/concentrations to purify the protein:

[0043] **As well known by the skilled person, chromatography uses the fact that proteins are multivalent anions or cations.** Due to the total charge (net charge) of the proteins it is possible to bind them to a charged stationary phase, as long as the salt concentration is kept low. Salt gradients are the

most common means of eluting proteins from ion exchangers. Excessively high salt concentrations cause shielding of the charges on the protein surface and effective binding to an exchanger can no longer take place. Since the bound proteins are subsequently displaced with the aid of an increasing salt gradient, proteins varying in charge can be separated. The action of the salts can be considered in one of two ways. The salt can directly displace the protein; the ions occupy the charged sites and block reattachment by protein. Alternatively, the system can be regarded as an equilibrium in which even strongly bound proteins spend some time not adsorbed; the presence of the salt ions between the unattached protein and the adsorbent weakens the attraction between the two. In either case, the desorbed proteins are replaced by counter-ions. **Elution of proteins can be carried by stepwise higher salt concentrations, or by linear or non-linear salt gradients.**

i) Grandics et al. also teach varying salt gradients to elute the protein during the wash phase (bottom col. 7 to top column 8):

Detailed Description Text - DETX (22):

2. In the event if HIC is preferred for the purification of the product, the 4 cartridge contains an appropriate medium, such as phenyl-, octyl-, butyl-, hexyl-, isopentyl-liganded or other HIC media. The 4 HIC cartridge is **equilibrated with the binding salt by using 70 gradient former.** The cell culture medium is then applied as described for the ion exchange chromatography separations. The binding salt is applied through 70 gradient former at the appropriate ratio. Unbound materials are washed with the binding salt solution and then product is recovered by applying a low salt buffer or a reverse salt gradient onto the 4 cartridge through the 70 gradient former.

III. Conclusion: The Examiner maintains the Office's position, that based on the teachings within the references, that washing using different salt gradients was known at the time of the invention, and employed within the prior art. And that varying the type of salt, amount (e.g. increasing OR decreasing concentration), gradient employed thereof – if Applicant's process does varies in any one or more of these routinely optimizable parameters from that of the prior art - would have been an obvious varying, depending on the other routinely optimizable aspect – the end product desired (e.g. protein concentration, amount).

Thus, on the specific issue of the increasing (or for that matter decreasing if ever desired) the salt concentration, along the washing steps, to purify the protein desired, the skilled artisan in protein purification (PhD in Peptide Chemistry) is well versed in this art-recognized technique employed in peptide purification techniques using salt gradients, including via ion exchange chromatography; as known in the art generally or by the combination of references applied on the record.

IV. The rejection and Applicant's previous arguments/response thereto are included below for continuity of record:

Applicant's summarized argument, throughout, including on page 6 under the 'improper hindsight' argument, is that the combination of Genetech and Grandics does not reasonably teach or suggest/motivate, and thus not render predictable, to one of ordinary skill in the art – "protein purification via cation exchange chromatography employing different salt gradients resulting in a non-linear salt gradient." Thus, if not well known in the art, as the Examiner has asserted, the Examiner has added the Winge to supplement the previous combination of references, in order to provide the express literature that such was known in the art and thus motivation/predictability present.

Genentech is discussed in the previous action, and as Applicant pointed out in the response of 6/12/06 (page 8), teaches protein purification by ion exchange chromatography (entire document). However, Basey et al. does not teach an ion exchange chromatography system where a salt gradient is employed (see Applicant's response page 9).

Grandics et al. teach the use of an integrated cell culture protein purification system using an ion exchange chromatography using a salt gradient (bottom col. 7 to top col. 8, entire document).

Winge, in his entitled patent publication, Protein Purification I, describes at para's 42-43, 63, and 81 (see also entire document), his version of "protein purification via cation exchange chromatography employing different salt gradients resulting in a non-linear salt gradient":

[0042] The said cation exchange step is carried out by adsorption chromatography, preferably column chromatography. In ion exchange chromatography, charged substances are separated via column materials that carry an opposite charge (see e.g. Scopes, R. K. Protein Purification, Principles and Practice, Third edition, Springer-Verlag 1993). The ionic groups of exchanger columns are covalently bound to the gel matrix and are compensated by small concentrations of counter ions, which are present in the buffer. When a sample is added to the column, an exchange with the weakly bound counter ions takes place.

[0043] As well known by the skilled person, chromatography uses the fact that proteins are multivalent anions or cations. Due to the total charge (net charge) of the proteins it is possible to bind them to a charged stationary phase, as long as the salt concentration is kept low. Salt gradients are the most common means of eluting proteins from ion exchangers. Excessively high salt concentrations cause shielding of the charges on the protein surface and effective binding to an exchanger can no longer take place. Since the bound proteins are subsequently displaced with the aid of an increasing salt gradient, proteins varying in charge can be separated. The action of the salts can be considered in one of two ways. The salt can directly displace the protein; the ions occupy the charged sites and block reattachment by protein. Alternatively, the system can be regarded as an equilibrium in which even strongly bound proteins spend some time not adsorbed; the presence of the salt ions between the unattached protein and the adsorbent weakens the attraction between the two. In either case, the desorbed proteins are replaced by counter-ions. Elution of proteins can be carried by stepwise higher salt concentrations, or by linear or non-linear salt gradients.

[0063] As shown in Example 1, Step 2, below, AT-III can be conveniently separated from HRGP, and thus purified, by the method as defined above. In a

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further aspect, this method includes the separation and purification of the AT-III isoforms AT-III.alpha. and AT-III.beta.. A protein solution mainly comprising AT-III.alpha. can be obtained by collecting a protein fraction, which is the earlier of two main protein fractions eluting from the gel under low ionic strength conditions. A protein solution mainly comprising AT-III can be obtained by collecting a protein fraction, which is the later of two main protein fractions eluting from the gel under low ionic strength conditions. In the Example below, retention times of 8 and 104 min for AT-III.alpha. and AT-III.beta., respectively, have been shown. However, the skilled person will understand that the retention time will depend on a number of factors, such as the pH and ionic strength of the elution buffer, temperature, column dimensions, protein load, and flow rate. General information on the effect of various parameters can be found in textbooks on protein purification, such as the one by Scopes (supra).

[0081] It will be understood by the skilled person that the starting solution may have to be treated in a suitable manner before contacting the said solution with a cation exchange gel. It is normal for the applied protein mixture to be in the same buffer used to equilibrate the column. Further, the pH and ionic strength should be similar or identical with the column buffer. There are two usual ways of attaining the correct buffer composition: dialysis or gel filtration (see e.g. Scopes, R. K. Protein Purification, Principles and Practice, Third edition, Springer-Verlag 1993). Alternatively, a suitable conductivity can be attained by dilution with distilled water, as in Example 1, step 4, below. A suitable pH value can be obtained by addition of a base such as sodium hydroxide or an acid such as citric acid.

Thus, if not well known by those of ordinary skill in the art, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use a salt gradient in the ion exchange chromatography system of protein purification, more specifically, carrying out "protein purification via cation exchange chromatography employing different salt gradients resulting in a non-linear salt gradient", in Genentech, because Grandics et al. advantageously teaches the use of a salt gradient in a similar ion exchange chromatography system for cell culture protein purification, and the use of the salt gradient for purifying any protein as in Genentech would have merely been a matter of optimization by a protein research

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scientist versed in the methods of protein purification, as guided by the results sought. But if not, Winge provides the express teachings regarding one version of "protein purification via cation exchange chromatography employing different salt gradients resulting in a non-linear salt gradient."

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's PREVIOUS arguments are included below for continuity of record, as summarized by the Examiner (p. 4 of response):

As Basey *et al.* (Genentech) does not employ a salt gradient and as Grandics *et al.* discloses the use of *only a single linear salt gradient* in protein purification, combination of the two references would not lead to the invention or to the superior results obtained using a non-linear gradient of increasing ionic strength. As the results obtained in the present application using non-linear gradient are unexpectedly superior over the results achieved or suggested by the combination of Basey *et al.* and Grandics *et al.*, the cited combination does not render obvious, the invention claimed in the present application.

It is acknowledged that Basey *et al.* does not teach a salt gradient, which was never disputed; hence Grandics *et al.* was cited to fill this void as known in the art. Thus, following the response, the only issue is whether one of skill in the art would have been motivated to use more than a linear salt gradient (e.g. single pass) in view of Grandics *et al.*? As noted above, Applicant's depiction of the present invention is that it involves a "non-linear (salt) gradient", as opposed to merely linear, and concludes that Grandics *et al.* only teaches a linear (single) pass

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gradient. Contrary to Applicant's conclusion, the Examiner's review of the reference does in fact find that Grandics et al. teaches a "non-linear (salt) gradient" option (see col. 7-8):

The binding salt is applied through 70 gradient former at the appropriate ratio. Unbound materials are washed with the binding salt solution and then product is recovered by applying a low salt buffer or a reverse salt gradient onto the 4 cartridge through the 70 gradient former.

Therefore, the rejection had been maintained for the reasons of record, and made Final.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MA, 12/20/2009

/Maury Audet/
Examiner, Art Unit 1654
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